April 07, 2008

Roger Citron, R.Ph.
1400 E Broadway St
PO Box 202951
Helena, MT 59601-5231

Dear Mr. Citron:

Your Senior Regional Scientific Manager, Randall Legg, has forwarded your request for information regarding SYMBICORT® (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol. The following information is attached for your review:

- **SYMBICORT-Comparison with Fixed Dose Regimens of Fluticasone Propionate/Salmeterol (Advair Diskus) or Advair HFA pMDI for Asthma**

The attached information is supplied to you as a professional courtesy in response to your request. It is intended to provide pertinent data to assist you in forming your own conclusions and making decisions. Prescription drugs used outside of their approved indication may not be eligible for reimbursement by any third-party payors, including Medicaid, Medicare, or similar federal or state programs. AstraZeneca does not recommend the use of SYMBICORT in any other manner than as described in the full prescribing information. Prescribing information for SYMBICORT may be obtained from www.astrazeneca-us.com or by calling the Information Center at AstraZeneca at 1-800-236-9933.

Thank you for your interest in SYMBICORT. If we may be of further assistance to you, please contact AstraZeneca at 1-800-236-9933.

Sincerely,

Debra A. Perlsweig, Pharm.D.

Senior Medical Information Manager

INQ 647097

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SYMBICORT–Comparison with Fixed Dose Regimens of Fluticasone Propionate/Salmeterol (Advair Diskus® or Advair® HFA pMDI) for Asthma

Summary

- In a 7-month open-label study, patients aged ≥ 12 years, with moderate to severe asthma requiring inhaled corticosteroid (ICS) therapy, 1 month of treatment with SYMBICORT pressurized metered-dose inhaler (pMDI) 160/4.5 mcg (2 actuations BID) or fluticasone propionate/salmeterol xinafoate combination (SFC; Advair Diskus®, GlaxoSmithKline) 250/50 mcg BID demonstrated no differences in efficacy for asthma exacerbations, predose forced expiratory volume in one second (FEV_1) or any measure of asthma control.[2] Safety profiles for both treatments were comparable.

- In two single-dose crossover studies, improvements in FEV_1 at 3 minutes post dose were significantly greater after a single treatment of SYMBICORT pMDI 80/4.5 mcg (2 actuations), compared with SFC 250/50 mcg ($p<0.001$). Treatment with SYMBICORT pMDI and albuterol 90 mcg (2 actuations) produced similar mean increases in FEV_1 at 3 minutes following a single dose of either drug.[6,7]

Prescribing Information[1]

SYMBICORT is available in 2 strengths, SYMBICORT 80/4.5 and SYMBICORT 160/4.5, containing 80 and 160 mcg of budesonide, respectively, and 4.5 mcg of formoterol fumarate dihydrate per inhalation. Each dose is administered as 2 inhalations twice daily (in the morning and the evening) by the orally inhaled route only. Rinsing the mouth after every dose is advised.

Indications And Usage

SYMBICORT is indicated for the long-term maintenance treatment of asthma in patients 12 years of age and older.

Long-acting $beta_2$-adrenergic agonists may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. SYMBICORT is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting $beta_2$-agonists.

SYMBICORT is NOT indicated for the relief of acute bronchospasm.

Onset of Action and Progression of Improvement

The onset of action and progression of improvement in asthma control were evaluated in the 2 pivotal clinical studies. The median time to onset of clinically significant bronchodilation (>15% improvement in FEV_1) was seen within 15 minutes. Maximum improvement in FEV_1 occurred

within 3 hours, and clinically significant improvement was maintained over 12 hours. Figures 3 and 4 show the percent change from baseline in post-dose FEV_1 over 12 hours on the day of randomization and on the last day of treatment for Study 1.

Reduction in asthma symptoms and in albuterol rescue use, as well as improvement in morning and evening PEF, occurred within 1 day of the first dose of SYMBICORT; improvement in these variables were maintained over the 12 weeks of therapy.

Following the initial dose of SYMBICORT, FEV_1 improved markedly during the first 2 weeks of treatment, continued to show improvement at the Week 6 assessment, and was maintained through Week 12 for both studies.

No diminution in the 12-hour bronchodilator effect was observed with either SYMBICORT 80/4.5 mcg or SYMBICORT 160/4.5 mcg as assessed by FEV_1 following 12 weeks of therapy or at the last available visit.

FEV_1 data from Study 1 evaluating SYMBICORT 160/4.5 mcg is displayed in FIGURE 3 and FIGURE 4.

FIGURE 3: Mean Percent Change From Baseline in FEV_1 on Day of Randomization (Study 1)

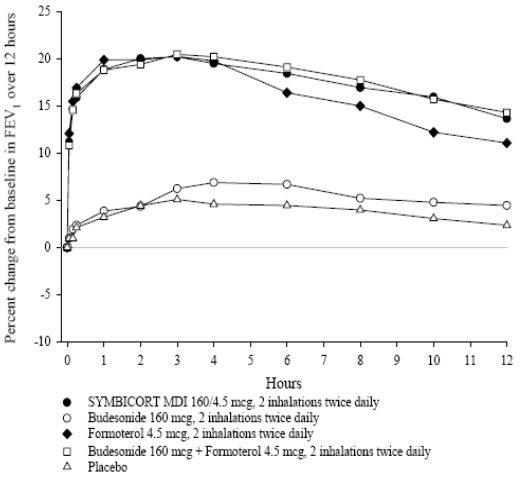
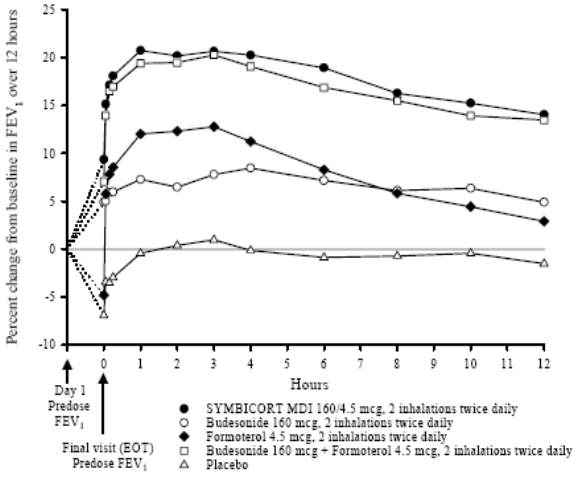


FIGURE 4: Mean Percent Change From Baseline in FEV_1 At End of Treatment (Study 1)



Clinical Data

A search of the biomedical literature failed to identify any studies published to date in which SYMBICORT pMDI has been directly compared to SFC 500/50 mcg (Advair Diskus®) mcg in a controlled clinical trial. In addition, a search of the biomedical literature failed to identify any citations comparing SYMBICORT pMDI to SFC hydrofluoroalkane (HFA) pMDI (Advair® HFA, GlaxoSmithKline).

SYMBICORT pMDI vs SFC

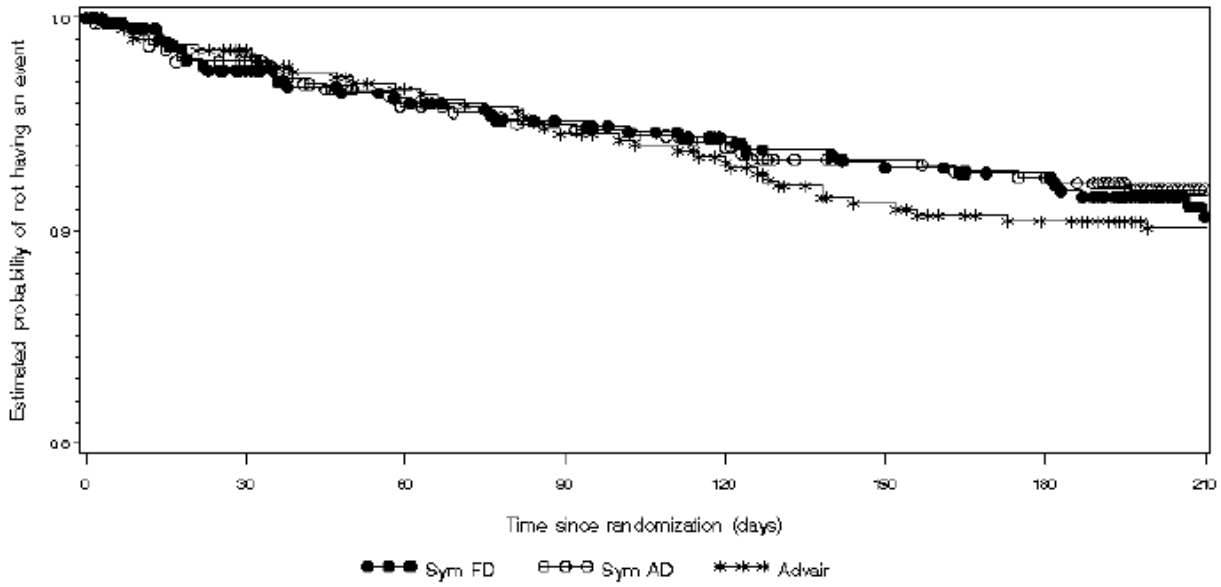
Three clinical studies, which incorporate treatment arms of SYMBICORT pMDI and SFC, have been conducted in the US.[2,6,7] All were submitted to the FDA in support of the SYMBICORT new drug application (NDA). There are no other studies comparing SYMBICORT pMDI to SFC.

A 7-month, randomized, parallel-group, open-label study (D5896C00005) was conducted to compare the efficacy and safety of SYMBICORT pMDI, administered as either a fixed-dose (FD) or adjustable dose (AD) regimen, with that of a FD regimen of SFC in 2080 patients ≥ 12 years with asthma requiring ICS or combination with long-acting beta-agonist (LABA) therapy.[2,3,4,5] Following a 10-14 day run-in, with their current therapy (mean total daily ICS dose at study entry between 538.9 mcg to 555.7 mcg), 1225 patients were randomized to receive FD SYMBICORT pMDI 160/4.5 mcg (2 actuations BID) or SFC 250/50 mcg (1 inhalation BID) for 1 month, as Treatment Period 1. At the end of Treatment Period 1, patients receiving SYMBICORT pMDI were randomized to either SYMBICORT pMDI FD or AD, while patients receiving SFC continued their study regimen, as Treatment Period 2, for an additional 6 months.

The primary efficacy endpoint was asthma control as measured by asthma exacerbations, defined as worsening asthma which required treatment with oral steroids, and assessed using time to first exacerbation; the number of exacerbations in each treatment group; and number (%) of subjects with at least 1 exacerbation. Secondary outcomes included predose FEV_1, morning peak expiratory flow (PEF), daytime and nighttime asthma symptom scores, nighttime awakenings due to asthma symptoms, daytime and nighttime rescue medication use, total daily rescue medication use and both physician and patient global assessment.

Time (in days) from the first dose of randomized treatment to the first exacerbation (primary efficacy endpoint) was analyzed using a log-rank test and also described using a Kaplan-Meier plot. (FIGURE I) Additionally, a Cox proportional hazards model was used to estimate hazard ratios. The number and percentage of subjects with at least 1 asthma exacerbation during randomized treatment was analyzed using a chi-square test. The number of exacerbations was expressed as the number per subject-treatment year and analyzed using a Poisson regression model adjusting for subject exposure. FIGURE I presents Kaplan-Meier probability curves for time in days to first asthma exacerbation during the overall randomized treatment period. TABLE I presents the survival analysis of time to first asthma exacerbation for the overall randomized treatment period.

FIGURE 1: Time (days) to first asthma exacerbation during the overall randomized treatment period: Kaplan-Meier probability curves (efficacy analysis set). Adapted from In House Data, AstraZeneca LP, D5896C00005.



Sym FD: SYMBICORT pMDI (fixed-dose) 160/4.5 mcg x 2 actuations twice daily; Sym AD: SYMBICORT pMDI (adjustable dose) 160/4.5 mcg x 2 actuations once daily, 160/4.5 mcg x 2 actuations twice daily, 160/4.5 mcg x 4 actuations twice daily; Advair: SFC Diskus 250/50 mcg x 1 inhalation twice daily.
Note: The first 30 days on this figure represents Treatment Period 1; this was approximately the timeframe during which subjects in the SYMBICORT pMDI AD group received fixed-dose SYMBICORT pMDI.

TABLE I: Survival Analysis of Time to First Asthma Exacerbation During the Overall Randomized Treatment Period (Efficacy Analysis Set). Adapted from In House Data, AstraZeneca LP, D5896C00005.

Treatment*/Treatment Comparison	n	Had Event, n (%)	Log-rank test	
			Chi-square	p value
Treatment				
SYMBICORT pMDI FD	422	37(8.8)		
SYMBICORT pMDI AD†	389	31(8.0)		
SFC	404	37(9.2)		
Treatment Comparison				
SYMBICORT pMDI FD vs SFC			0.003	0.958
SYMBICORT pMDI FD vs SYMBICORT pMDI AD			0.389	0.533
SYMBICORT pMDI AD vs SFC			0.467	0.494

* SYMBICORT pMDI FD (fixed-dose) 160/4.5 mcg x 2 actuations twice daily; SYMBICORT pMDI AD (adjustable-dose) 160/4.5 mcg x 2 actuations once daily, 160/4.5 mcg x 2 actuations twice daily, 160/4.5 mcg x 4 actuations twice daily; SFC Advair Diskus 250/50 mcg x 1 inhalation twice daily; †Subjects in the adjustable-dose group received approximately 1 month of fixed-dose SYMBICORT pMDI during Treatment Period 1.
Note: The overall randomized treatment period included both Treatment Period 1 and Treatment Period 2.

No differences in efficacy among the 3 treatment groups were seen for the primary endpoint, asthma exacerbation, or for secondary endpoints of predose FEV_1 and morning PEF or any measure of asthma control after up to 7 months of treatment.

All 3 treatments were well tolerated and the percentage of subjects reporting an adverse event (AE) during the treatment periods was similar across treatment groups. The most common AEs occurring with an incidence of ≥ 5% in any treatment group include headache, nasopharyngitis, sinusitis, upper respiratory tract infection, pharyngolaryngeal pain and asthma. The incidence of asthma and potentially asthma-related AEs, and of cardiac AEs was generally low and similar across treatment groups. The percentage of patients experiencing serious adverse events (SAEs) was low and similar across treatment groups. Discontinuation of treatment due to adverse event (DAEs) was also low among treatment groups, however, slightly higher in the FD SYMBICORT pMDI group compared with the AD SYMBICORT pMDI and SFC groups. Headache was the most commonly reported DAE, occurring in 4 patients in the FD SYMBICORT pMDI group (0.9%) and in 1 patient in the AD SYMBICORT pMDI group (0.3%). A total of 3 DAEs due to asthma were seen in the SFC group (n=2, 0.5%) and the FD SYMBICORT pMDI group (n=1, 0.2%).

There was 1 reported asthma-related hospitalization in the FD SYMBICORT pMDI group, 1 in the AD SYMBICORT pMDI group and 3 in the SFC group. The differences were not statistically significant. The incidence of oral candidiasis in this study was low, with no reports in the FD or AD SYMBICORT pMDI groups and 0.2% of patients reporting in the SFC group. The total number and percentage of subjects with the most commonly reported AEs, n (%) are shown in TABLE II.

TABLE II: Number (%) of Subjects with the Most Commonly Reported Adverse Events by Preferred Term During the Overall Randomized Treatment Period (Safety Analysis Set) Adapted from In House Data, AstraZeneca LP, D5896C00005.

Preferred term*	**Treatment group†, n (%) of subjects**		
	SYMBICORT pMDI FD (n=427)	**SYMBICORT pMDI AD (n=389)**	**SFC (n=406)**
Mean duration of exposure (days)	182.0	196.1	191.3
Total number of subjects with any AE, n (%)	263(61.6)	225(57.8)	238(58.6)
Headache	51 (11.9)	45 (11.6)	39 (9.6)
Nasopharyngitis	35 (8.2)	33 (8.5)	33 (8.1)
Sinusitis	37 (8.7)	28 (7.2)	31 (7.6)
Upper respiratory tract infection	31 (7.3)	31 (8.0)	34 (8.4)
Pharyngolaryngeal pain	29 (6.8)	22 (5.7)	24 (5.9)
Asthma	18 (4.2)	19 (4.9)	23 (5.7)
Bronchitis	14 (3.3)	10 (2.6)	16 (3.9)
Cough	21 (4.9)	7 (1.8)	11 (2.7)
Nasal congestion	14 (3.3)	10 (2.6)	8 (2.0)
Dysphonia	14 (3.3)	7 (1.8)	3 (0.7)

SYMBICORT pMDI FD (fixed-dose) 160/4.5 mcg x 2 actuations twice daily; SYMBICORT pMDI AD (adjustable-dose) 160/4.5 mcg x 2 actuations once daily, 160/4.5 mcg x 2 actuations twice daily, 160/4.5 mcg x 4 actuations twice daily; SFC Advair Diskus 250/50 mcg x 1 inhalation twice daily; †Based on MedDRA Version 8.0. Note: "Most commonly reported" refers to AEs reported by at least 3% of subjects in any treatment group, sorted by decreasing order of frequency across all treatment groups (total). The overall randomized treatment period includes both Treatment Periods 1 and 2. The SYMBICORT pMDI AD group received approximately 1 month of SYMBICORT pMDI FD during Treatment Period 1.

Two randomized, multicenter, placebo- and active-controlled, single-dose, 4-period, crossover studies (SD-039-0732 and SD-039-0733) were conducted to compare the early bronchodilatory effects of SYMBICORT pMDI 80/4.5 mcg (2 actuations), SFC 250/50 mcg, albuterol 90 mcg (2

actuations; Ventolin® HFA, Schering) and placebo.[6,7,8] Asthmatic patients ≥18 years old with FEV_1 percent predicted values of ≥ 0% and ≤95%, and reversibility of at least 15% (≥ 0.20 L) within 15 – 30 minutes of 2 to 4 actuations of albuterol, were enrolled in the studies. Fifty-five patients (aged 18 to 69; mean age 41 years) and 54 patients (aged 18 to 68; mean age 39 years) participated in studies 1 and 2, respectively. Following a 14±7 day run-in period, during which patients were maintained on budesonide pMDI 160/9 mcg BID and all other maintenance medications were stopped, patients participated in a 4-period treatment phase, with single dose treatments of SYMBICORT, SFC Diskus, albuterol or placebo, each separated by a 3 to 14 day washout period.

The primary variable was effect on FEV_1 at 3 minutes post dose of study medication. Improvements in FEV_1 at 3 minutes post dose were significantly greater after treatment with SYMBICORT pMDI compared with SFC Diskus ($p<0.001$). Treatment with SYMBICORT pMDI and albuterol produced similar mean increases in FEV_1 at 3 minutes post dosing. All active treatments demonstrated significantly greater increases in FEV_1 at 3 minutes post dose compared with placebo ($p\leq0.029$). Results are provided in TABLE III.

TABLE III: Mean changes in FEV_1 at 3 minutes post-dose. Adapted from In House Data, AstraZeneca LP, SD-039-0732 and In House Data, AstraZeneca LP, SD-039-0733.

	Mean FEV_1 in Liters (SD)				**Mean difference between groups (95% CI)**		
	SYMBICORT	**SFC**	**ALB**	**PBO**	**SYMBICORT – SFC**	**SYMBICORT – ALB**	**SYMBICORT – PBO**
Study 1	n=47	n=46	n=49	n=47			
Predose	2.46 (0.76)	2.45 (0.73)	2.38 (0.73)	2.46 (0.69)			
3-min post dose	2.67 (0.81)	2.50 (0.74)	2.63 (0.76)	2.43 (0.70)	0.17 (0.12, 0.23)*	-0.03 (-0.09, 0.03)	0.24 (0.18, 0.30)*
Study 2	n=45	n=48	n=47	n=49			
Predose	2.52 (0.64)	2.49 (0.63)	2.48 (0.67)	2.49 (0.71)			
3-min post dose	2.75 (0.70)	2.54 (0.65)	2.75 (0.74)	2.47 (0.72)	0.20 (0.14, 0.25)*	-0.04 (-0.10, 0.02)	0.26 (0.20, 0.32)*
	Mean FEV_1 in Liters (SD)				**Mean difference between groups (95% CI)**		
	SYMBICORT	**SFC**	**ALB**	**PBO**	**SYMBICORT – SFC**	**SYMBICORT – ALB**	**SYMBICORT – PBO**
Combined	n=92	n=94	n=96	n=96			
Predose	2.49 (0.70)	2.47 (0.68)	2.43 (0.70)	2.47 (0.69)			
3-min post dose	2.71 (0.76)	2.52 (0.69)	2.69 (0.75)	2.45 (0.71)	0.18 (0.14, 0.22)*	-0.04 (-0.08, 0.00)	0.25 (0.21, 0.29)*

SD = Standard deviation; CI = Confidence Interval; SYMBICORT = BUD/FOR pMDI; SFC = fluticasone/salmeterol DPI, ALB = albuterol pMDI, PBO = placebo pMDI; * $p<0.001$

Secondary efficacy variables included FEV_1 at 9, 15, and 30 minutes, and 1, 2, 3, 4, 6, 8, 10, and 12 hours post dose; average FEV_1 over the 12-hour post dose period, average FEV_1 over 0 to 6 hours post dose, and average FEV_1 over 6 to 12 hours post dose, each calculated as an area under the FEV_1-time-curve divided by observation time; maximum FEV_1 over the 12-hour post dose period; and the percentage of patients achieving ≥15% and ≥12% increase in FEV_1 over the first 60 minutes post dose.

Significantly more patients treated with SYMBICORT achieved both the 15% and 12% thresholds for improvement within 15 minutes compared with SFC Diskus ($p<0.001$). At 1 hour postdose, the percentages of patients treated with SYMBICORT pMDI who achieved ≥15% and ≥12% improvements in FEV_1 were similar compared with patients treated with albuterol pMDI and SFC Diskus, however were significantly greater compared with placebo (3.0% and 7.0%) ($p<0.001$).

Mean changes in FEV_1 over the 12-hour post dose period for the SYMBICORT pMDI and SFC Diskus groups were similar in Study 1 and Study 2. Results are provided in the table below.

TABLE IV: Maximum Mean 12-hour Post Dose FEV_1. Adapted from In House Data, AstraZeneca LP, SD-039-0732 and In House Data, AstraZeneca LP, SD-039-0733.

	Mean FEV_1 in Liters (SD)				**Mean difference between groups (95% CI)**		
	SYMBICORT	**SFC**	**ALB**	**PBO**	**SYMBICORT - SFC**	**SYMBICORT - ALB**	**SYMBICORT - PBO**
Study 1	n=49	n=51	n=52	n=51			
Predose	2.45 (0.75)	2.43 (0.72)	2.41 (0.72)	2.45 (0.70)			
12 hours post dose	2.90 (0.80)	2.87 (0.82)	2.88 (0.79)	2.65 (0.75)	0.11 (-0.05, 0.07)	0.00 (-0.06, 0.06)	0.25 (0.19, 0.31)*
Study 2	n=45	n=49	n=48	n=49			
Predose	2.52 (0.64)	2.46 (0.65)	2.49 (0.67)	2.49 (0.71)			
12 hours post dose	3.03 (0.73)	2.93 (0.71)	2.94 (0.76)	2.75 (0.75)	0.05 (0.0, 0.10)†	0.04 (-0.01, 0.09)	0.24 (0.19, 0.29)*
Combined	n=94	n=100	n=100	n=100			
Predose	2.49 (0.70)	2.45 (0.68)	2.45 (0.69)	2.47 (0.70)			
12 hours post dose	2.96 (0.76)	2.90 (0.76)	2.91 (0.77)	2.69 (0.75)	0.03 (-0.01, 0.07)	0.02 (-0.02, 0.06)	0.25 (0.21, 0.29)*

*$p<0.001$; †$p<0.05$

Overall, the authors concluded that treatments were well tolerated in both studies, with 25.5% (14/55) and 37% (20/54) of patients reporting an AE.

Other Formulations of Formoterol/Budesonide

A search of the biomedical literature revealed several citations comparing SYMBICORT TURBUHALER, (formulation not available in the US), to SFC. This search includes a citation comparing SYMBICORT TURBUHALER as maintenance and reliever therapy (M & R) to a higher fixed maintenance dose of SYMBICORT TURBUHALER. The resultant bibliography with custom abstracts, where available, has been attached for your review. This should not be viewed as a comprehensive collection of all the relevant citations concerning this subject.

Reference(s):

[1] SYMBICORT Prescribing Information.
[2] In House Data, AstraZeneca LP, D5896C00005.

[3] Busse WW, Shah SR, Somerville L, et al. Comparison of asthma exacerbations and lung function with adjustable-dose budesonide/formoterol pressurized metered-dose inhaler (BUD/FM pMDI), fixed-dose BUD/FM pMDI, and fixed-dose fluticasone/salmeterol dry powder inhaler (FP/SM DPI) [abstract]. *Proc Am Thorac Soc*. 2007;A191.
[4] Somerville L, Busse WW, Shah SR, et al. Safety of adjustable-dose budesonide/formoterol pressurized metered-dose inhaler (BUD/FM pMDI), fixed-dose BUD/FM pMDI, and fixed-dose fluticasone (FP)/salmeterol (SM) dry powder inhaler (DPI) in asthma patients [abstract]. *Proc Am Thorac Soc*. 2007;A191.
[5] Shah SR, Busse WW, Somerville L. Asthma control with adjustable and fixed-dose budesonide/formoterol pressurized metered-dose inhaler (BUD/FM pMDI) and fixed-dose fluticasone/salmeterol dry powder inhaler (FP/SM DPI) [abstract]. *Proc Am Thorac Soc*. 2007;A192.
[6] In House Data, AstraZeneca LP, SD-039-0732.
[7] In House Data, AstraZeneca LP, SD-039-0733.
[8] Hampel Jr FC, Martin P, Mezzanotte WS. Early bronchodilatory effects of budesonide/formoterol pressurized metered-dose inhaler (pMDI) compared with fluticasone propionate/salmeterol dry powder inhaler (DPI) and albuterol pMDI in adults with asthma [abstract]. *J Allergy Clin Immunol*. 2008;121(2 Suppl 1):S220-S1, Abs 849.

Literature Search:
Terms: (SYMBICORT or budesonide/formoterol or formoterol/budesonide) and (Advair or salmeterol/fluticasone or fluticasone/salmeterol) and asthma
PL@NET, Ovid
February 2008

Aalbers R, Backer V, Kava TTK, et al. Adjustable maintenance dosing with budesonide/formoterol compared with fixed-dose salmeterol/fluticasone in moderate to severe asthma. *Curr Med Res Op*. 2004;20:225-240.

Custom abstract: This randomized, double-dummy, double-blind/open-extension, parallel-group, multicenter study aimed to determine whether adjustable maintenance dosing (AMD) of the combination inhaler Symbicort Turbuhaler (budesonide/formoterol) 160/4.5 mcg improved control of moderate-to-severe asthma compared with traditional fixed dosing (FD) regimens (budesonide/formoterol or Seretide (salmeterol/fluticasone)) in 658 outpatients. Previous studies are cited in the introduction which found that budesonide/formoterol AMD significantly improved asthma control compared with budesonide/formoterol FD, and also found the AMD regimen to result in lower drug costs (Fitzgerald et al., 2003; Olsson et al., 2003). All patients had used inhaled corticosteroids for ≥ 3 months before study entry at a constant daily dose within the last month (500-1200 mcg for budesonide, based on metered dose) without concomitant long-acting beta-agonists. In the 10-14 day-run in, the 1044 enrolled patients continued with inhaled corticosteroid therapy with Bricanyl Turbuhaler (terbutaline sulfate) or salbutamol reliever medication prn, and 658 patients were randomized in the 1-month double-blind period of the study to receive budesonide/formoterol AMD 160/4.5 mcg 2 inhalations twice daily (n = 219; 94 male, 125 female; aged 12-76 years), budesonide/formoterol FD 160/4.5 mcg 2 inhalations twice daily (n = 215; 96 male, 119 female; aged 13-85 years), or salmeterol/fluticasone FD 1 inhalation twice daily via Diskus (n = 224; 109 male, 115 female; aged 14-78 years). The total daily dose of budesonide/formoterol was 640/18 mcg/day. During the 6-month open-extension period of the study, the budesonide/formoterol FD and salmeterol/fluticasone groups continued to use 2 inhalations twice daily while the budesonide/formoterol AMD group were instructed to use either 1 or 2 inhalations twice daily with increases to 4 inhalations twice daily depending on the level of asthma control. All budesonide/formoterol AMD patients recorded reliever medication consumption and nighttime awakenings on a diary card, which was reviewed by the investigator, and the patient's medication was then adjusted according to symptom control. Morning and evening PEFR and FEV_1 were also measured. 654 patients were analyzed for primary outcome. 71% of patients experienced at least 1 night-time awakening during the last 10 days of run-in (mean of 2.4 nights/weeks) and high adherence was self-reported by patients on their diary cards. Similar odds of achieving a well-controlled asthma week (WCAW) were found in both FD groups, and although there was an increase in the odds of achieving a WCAW in the budesonide/formoterol AMD group during the open extension compared with budesonide/formoterol FD, no improvement was seen compared with salmeterol/fluticasone FD. One-fifth of patients across all groups failed to achieve a single WCAW. No treatment differences were observed for the composite total asthma control weeks (TACW) measure: no TACWs were achieved in the run-in period and only 18-21% of patients achieved TACW in the 3 groups compared with 47-54% of patients who achieved WCAW. The budesonide/formoterol AMD group experienced fewer asthma exacerbations than either of the other 2 groups, and a significant reduction was noted in favor of the budesonide/formoterol FD and AMD groups compared with salmeterol/fluticasone FD; however, the difference between the 2 budesonide/formoterol groups was non-significant. Asthma symptoms and reliever use were lower during the exacerbation period in both budesonide/formoterol FD and AMD groups. FEV_1 significantly improved following 1 months of budesonide/formoterol FD double-blind treatment compared with salmeterol/fluticasone, and was maintained during the 6-month extension, although no other differences were observed. After switching from an FD regimen to 6 months of AMD treatment, budesonide/formoterol AMD patients used their reliever medication less frequently than those who continued with the FD regimen, and night-time awakenings and evening PEFR were also significantly

reduced among budesonide/formoterol who switched from FD to AMD. Sufficient asthma control was obtained by 45% of the budesonide/formoterol AMD group after the 1-month double-blind period, enough to warrant a reduction in maintenance treatment from 2 inhalations to 1, and 57% of budesonide/formoterol AMD patients did not required a treatment step-up: those who did require a step-up in this group regained control of their asthma within 7 days. On average, fewer study drug inhalations and long-acting beta agonists were taken in the budesonide/formoterol AMD group compared with the budesonide/formoterol FD group. Budesonide/formoterol FD and salmeterol/fluticasone FD showed no clear cost differences, but budesonide/formoterol AMD resulted in consistently lower drug costs in 5 EU markets. The incidence of adverse events was similar in all groups, and most were mild or moderate: however, a higher incidence of dysphonia and candidiasis was noted in the salmeterol/fluticasone FD groups than either of the budesonide/formoterol regimens. A total of 31 serious adverse events occurred in 8 budesonide/formoterol AMD patients, 11 budesonide/formoterol FD patients and 5 salmeterol/fluticasone patients, but none were attributed to the drugs. The authors conclude that the budesonide/formoterol AMD regimen was well tolerated and more effective than traditional fixed dosing with either budesonide/formoterol or salmeterol/fluticasone.

Bousquet J, Boulet L-P, Peters MJ, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. *Resp Med*. 2007;101:2437-2446.

Dahl R, Chucahlin A, Gor D, et al. EXCEL: A randomized trial comparing salmeterol/fluticasone propionate and formoterol/budesonide combinations in adults with persistent asthma. *Resp Med*. 2006;100:1152-1162.

Fitzgerald JM, Boulet LP, Follows RMA. The CONCEPT trial: A 1-year, multicenter, randomized, double-blind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of formoterol/budesonide in adults with persistent asthma. *Clin Ther.* 2005;27:393-406.

Kuna P, Peters MJ, Manjra AI, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Prac*. 2007;61:725-736.

Palmqvist M, Arvidsson P, Beckman O, et al. Onset of bronchodilation of budesonide/formoterol vs. salmeterol/fluticasone in single inhalers. *Pulm Pharmacol Ther*. 2001;14:29-34.

Custom Abstract: The intent of this double-blind, randomized, placebo-controlled crossover study was to investigate the onset of action of Symbicort Turbuhaler (budesonide and formoterol) in a single inhaler and that of the fixed combination of Seretide Diskus (salmeterol and fluticasone) in 30 patients (15 male, 15 female; aged 23-73 years). All patients showed a post-bronchodilatory increase in FEV_1 after inhalation of 100 mcg Inspiryl Turbuhaler (salbutamol) or after an additional 400 mcg salbutamol. Patients received either placebo or budesonide/formoterol 160/4.5 mcg (1 inhalation), budesonide/formoterol 160/4.5 mcg (2 inhalations), or salmeterol/fluticasone 50/250 mcg. It was observed that both doses of the budesonide/formoterol combination produced a faster onset of improvement in FEV_1 compared with the salmeterol/fluticasone combination. A total of 47% of the patients demonstrated an onset of effect (15%) after inhalation of salmeterol/fluticasone. In the budesonide/formoterol group, 22 patients (73%) demonstrated an onset of effect after 1 dose and 23 patients (77%) after 2 doses. There were no definitive results indicating any variation between the 2 budesonide/formoterol doses for changes in FEV_1, up to 3 h after inhalation. The authors conclude that the combination of budesonide/formoterol has a faster onset of action compared with salmeterol/fluticasone.

Peters M, Bousquet J. Episodic high reliever use with budesonide/formoterol maintenance and reliever therapy confers added protection against asthma exacerbation [abstract]. *Eur Resp J*. 2007;30(suppl 51):Abs 3613.

Custom abstract: In this randomized study, the authors determine whether high reliever use during periods of unstable asthma is clinically beneficial in a number of patients with asthma (n=2309). The patients were randomly assigned to receive either budesonide formoterol maintenance and reliever therapy (Symbicort SMART) 2 x 160 mcg/4.5 mcg plus 160 mcg/4.5 mcg prn or high-dose salmeterol/fluticasone 50 mcg/500 mcg twice daily plus terbutaline prn for a period of 6 months. It was found that budesonide/formoterol was highly effective in reducing exacerbations at a lower inhaled corticosteroid load when compared with high-dose salmeterol/fluticasone, and that

patients with episodes of high reliever use had higher exacerbation rates when compared with the full population.